



UNIVERSITI PUTRA MALAYSIA

**MOLECULAR DYNAMICS SIMULATIONS OF OLEYL OLEATE
NANO-EMULSION SYSTEMS**

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**MOLECULAR DYNAMICS SIMULATIONS OF OLEYL OLEATE NANO-
EMULSION SYSTEMS**

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in
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Abstract of the thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the Degree of Master of Science.

Molecular Dynamics Simulations of Oleyl Oleate Nano-emulsion Systems

By

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November 2009

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Problems associated with transdermal drug delivery were directly associated with the skin barrier which is the lipid bilayer at the *stratum corneum*. Chemical penetration enhancers provide effective solution to these problems. In this research, the potentials of the nano-emulsions of palm-based esters to act as chemical penetration enhancers were studied using computer simulations. The structural and dynamical properties of the nano-emulsions were studied using molecular dynamics simulation (MD) method as the research was focused on the structure of swollen micelles that resulted from solubilization of surfactants in the nano-emulsions system. The micelle system studied consisted of oleyl oleate (OE) with non-ionic surfactants, Span 20 (S20) and Tween 80 (T80) which was simulated in the presence of explicit solvent. Five sets of simulations

were performed to determine the most suitable composition for OE/S20 swollen micelles system. The Critical Mixed Micelle Concentration (CMMC) was determined at the region of 10% to 20% of micelle composition by measuring the surface tension of each composition studied. The simulation showed the tendency of OE/S20 mixture to form a cylindrical micelle structure. The stability of OE/S20 swollen micelle system under different temperatures was investigated by running MD simulation on OE/S20 swollen micelle at 300K, 350K and 400K. Temperature at 350K and 400K exhibited expansion of the micelle structure and was explained by the analysis of the radius of gyration (R_g) and radial distribution function $g(r)$ after 2.5 ns of simulation along with the entropy calculations. The effect of different hydrophobicity and hydrophilicity of the non-ionic surfactants used in the formulation of the nano-emulsions was described by the gyration plot and the eccentricity calculation. OE/T80 swollen micelle system exhibited the lowest eccentricity value and smallest in size (± 0.1 nm) compared to OE/S20 swollen micelle with the same number of molecules. The self-assembly profile of OE/T80 swollen micelles system was evaluated until 20 ns MD simulation which showed positive results with spherical micelle as the end product. The aggregate size distribution pattern explained the self-assembly characteristics of the swollen micelles system. However, the reverse-formation that one would expect in such system was not observed throughout 20 ns of MD simulation. Several properties such as hydrophobic mechanism, shapes and sizes of the resulting structure suggested that OE swollen micelles produced can be utilized as chemical penetration enhancers for transdermal drug delivery.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains.

Simulasi Dinamik Molekul Sistem Nano-emulsi Olil Oleat

Oleh

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Permasalahan berkaitan dengan penghantaran ubatan melalui kaedah transdermal adalah berkait terus dengan lapisan pelindung kulit dwilapis lipid di *stratum corneum*. Bahan kimia peningkat penerobosan memberi jawapan efektif kepada masalah ini. Di dalam penyelidikan ini, potensi untuk nano-emulsi daripada ester kelapa sawit untuk bertindak sebagai bahan kimia peningkat penerobosan dikaji menggunakan simulasi komputer. Sifat struktur dan dinamik nano-emulsi dikaji menggunakan kaedah simulasi Dinamik Molekul (MD) yang mana kajian ini memfokuskan kepada struktur misel berkembang yang terhasil daripada pemelarutan surfaktan di dalam nano-emulsi berkenaan. Sistem misel yang dikaji membabitkan olil oleat (OE) serta surfaktan bukan ionik Span 20 (S20) dan Tween 80 (T80) di mana ianya disimulasikan dengan kehadiran pelarut nyata. Lima set simulasi telah dijalankan untuk mengetahui komposisi yang paling sesuai untuk sistem misel berkembang OE/S20. Kepekatan Kritikal Misel Campuran (CMMC) telah ditentukan di dalam kawasan 10% hingga 20% komposisi misel dengan mengukur

ketegangan permukaan untuk setiap sistem yang dikaji. Simulasi menunjukkan bahawa misel terkembang OE/S20 cenderung untuk membentuk struktur misel silinder. Kestabilan misel terkembang OE/S20 di bawah suhu yang berlainan telah diasas dengan mengaplikasikan simulasi MD ke atas misel terkembang OE/S20 pada suhu 300K, 350K dan 400K. Suhu pada 350K dan 400K menunjukkan pengembangan terhadap struktur misel dan diperjelaskan dengan analisis jejari putaran (R_g) dan fungsi pembahagian radial $g(r)$ selepas 2.5 ns berserta pengiraan entropi. Kesan perbezaan kehidrofilikan dan kehidrofobikan surfaktan bukan ionik yang digunakan di dalam formulasi nano-emulsi telah digambarkan melalui plot putaran dan pengiraan kesasaran. Sistem misel terkembang OE/T80 mempamerkan kesasaran yang paling rendah dan mempunyai saiz yang lebih kecil (± 0.1 nm) berbanding dengan sistem misel terkembang OE/S20 yang mengandungi jumlah molekul yang sama. Profil perhimpunan-sendiri sistem misel terkembang OE/T80 telah dipelajari melalui simulasi MD selama 20 ns dan ianya menunjukkan keputusan positif dengan pembentukan misel sfera sebagai hasil akhir simulasi. Corak pengagihan saiz gumpalan menerangkan tindak-tanduk perhimpunan-sendiri misel terkembang tersebut. Walau bagaimanapun, perhimpunan-berbalik yang dijangka akan berlaku tidak dapat dilihat dalam tempoh 20 ns simulasi MD. Berberapa sifat seperti mekanisma hidrofobik, saiz dan bentuk struktur yang dihasilkan mencadangkan bahawa misel terkembang OE boleh digunakan sebagai bahan peningkat penerobosan kimia untuk pengangkutan ubat secara transdermal.

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I certify that an Examination Committee met on **9th November 2009** to conduct the final examination of Muhammad Alif Mohammad Latif on his degree thesis entitled '**Molecular Dynamics Simulations of Oleyl oleate Nano-emulsion Systems**' in accordance with Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that candidate awarded the Master of Science (Computational and Theoretical Chemistry).

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DECLARATION

I hereby declare that this thesis is based on my original work except for quotations and citations which have been duly acknowledged. I also concur that it has not been previously or concurrently submitted for any other degree at UPM or other institutions.

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LIST OF ABBREVIATIONS

CMC	Critical Micelle Concentration
CMMC	Critical Mixed Micelle Concentration
CPE	Chemical Penetration Enhancer
EO	Ethylene oxide
FFTW	Fast Fourier Transform in the West
GROMACS	Groningen Machine for Computer Simulations
HLB	Hydrophile-Lipophile Balance
MD	Molecular Dynamics
NPT	Number, Pressure, Temperature
NVT	Number, Volume, Temperature
OE	Oleyl oleate
OPLS-AA	Optimized Potential for Liquid Simulation - All Atom
PME	Particle Mesh Ewald
RMSD	Root Mean Square Deviation
S20	Span 20 or sorbitan monolaurate
SANS	Small Angle Neutron Scattering
SAXS	Small Angle X-ray Scattering
T80	Tween 80 or Polysorbate 80
VMD	Visual Molecular Dynamics

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CHAPTER 1

INTRODUCTION

Transdermal drug delivery is capable of avoiding many problems associated with the oral routes but the major problem for this delivery system is overcoming the skin barriers which are lipid bilayers at the *stratum corneum*. While the skin barrier provides a significant challenge, the drug delivery can be improvised by understanding the mechanisms by which compounds cross the skin (Kogan and Garti, 2006). Research in the area of penetration enhancement or retardation is yielding valuable insights into the structure–activity relationships of enhancers as well as retardants. Traditionally, penetration enhancers were designed to deliver high drug concentrations across the skin into the systemic circulation.

Nowadays, chemical penetration enhancers (CPE) are widely studied and applied for transdermal drug delivery systems (Vàurovà *et al.*, 2005). Therefore, it is important to understand the behavior of these penetration enhancers at each level of their organization. Nano-emulsions of palm-oil esters are potentially a type of good CPE due to the lipophilic properties of palm-oil esters molecules (Sulaiman *et al.*, 2005). This research aimed to discover the structural properties of swollen or expanded micelles produced from palm-based nano-emulsions such as oleyl oleate nano-emulsions. The palm-based nano-emulsions swollen micelles system can be described structurally as dispersions on self-assembled or self-aggregated molecules of palm oil esters and

surfactants in water resulting from solubilization of surfactant aggregates in the nano-emulsions system. As a part of a nano-emulsions system, the characteristics of these swollen micelles are in such interests in structural and dynamics point of view. Such structure of the self-assembled molecules like spherical and cylindrical micelle is superior for a good CPE structural property due to its size (permeability), mobility of the drug inside and the release of drug (Peltola *et al.*, 2003). It is important to at first, to determine the structural properties without the drug itself. However, it is restricted for experimental work to gain accurate data during the micellization process such as the size variation, reactions involved and other physical, structural and dynamical properties.

The way that most researchers currently estimate the shape and structural properties of this system is by observing the spectrum data of such instruments like Small Angle Neutron and X-ray Scattering (SANS and SAXS). These spectrums however do not precisely describe the properties of the nano-emulsions when the size is too small (in nm range). More detailed studies can be done regarding the mechanism of action of the micelle system by using computational approach which is proven to be useful to predict and simulate the behavior of these chemical penetration enhancers at higher detail level (Wahab *et al.*, 2001). One of the approaches is the use of statistical calculations of selected force fields based on Newton's laws of motion which are called molecular dynamics (MD). By utilizing MD, computer-predictive information can be obtained on the structural and dynamics of the swollen micelles system.

This research focused on the investigation of oleyl oleate (OE) swollen micelles system in its nano-emulsions droplets which comprised of OE, non-ionic surfactants and water molecules. The properties of OE swollen micelles will be characterized by performing MD simulations as the molecules self-assemble into micellar aggregates in the presence of water as the solvent. OE is wax ester that has been widely used in cosmetic, pharmaceutical and lubricant industries. It has the lipophilic characteristics which identify the whole structure as hydrophobic. OE can be synthesized by enzymatic reaction of oleic acid and oleyl alcohol (Basri *et al.*, 2005).

In the nano-emulsions formulations, non-ionic surfactants were used to reduce the interfacial tension between oil phase and water by applying its amphiphilic properties. These surfactants represent the type of non-toxic surfactants that have been used for the solubilization of drugs for oral, topical and ocular administration (El-Sabbagh *et al.*, 1978). Sorbitan monolaurate, also commercially known as Span 20 (S20) is a partial ester of lauric acid with sorbitol and its mono- and di- anhydrides with edible lauric acid. It has the Hydrophilic-Lipophilic Balance (HLB) value of 8.6 ± 1.0 and dispersible in hot and cold water. Other non-ionic surfactant that was used in this project was Polysorbate 80 (commercially also known as Tween 80) is a non-ionic surfactant and emulsifier derived from polyethoxylated sorbitan and oleic acid, and is often used in foods. In pharmaceutical, Tween 80 (T80) with the reported HLB value of 15.0 ± 1.0 is used as an emulsifier in the manufacture of medications for parenteral administration, most notably in the popular anti-arrhythmic amiodarone.

1.1 Research Objectives

The purpose of this research is to utilize computational approach in order to characterize the structure and dynamics of oleyl oleate swollen micelles system in its nano-emulsions system. Therefore, the following objectives must be achieved:

1. To model the structure of oleyl oleate swollen micelles and characterize the system using molecular dynamics (MD) simulations method.
2. To utilize the use of MD simulations in determining the critical micelle concentration as well as analyzing the effect of composition and temperature to the micelle structure.
3. To verify the outcome of different HLB value of non-ionic surfactants to the structure of oleyl oleate swollen micelles.
4. To model and analyze the self-assembly of oleyl oleate swollen micelles system.

CHAPTER 2

LITERATURE REVIEW

2.1 Transdermal Drug Delivery

Drug molecules that are in contact with the skin surface can penetrate by three potential pathways: through the sweat ducts, through the hair follicles and sebaceous glands, or directly across the *stratum corneum* (Figure 1) (Benson, 2005). *Stratum corneum* in fact is the outer most layer of skin, which act as a physical barrier to most material that comes in contact with the skin. Substantial research attempt has been aimed at gaining better understanding of the structure and the unique barrier properties of the *stratum corneum*.

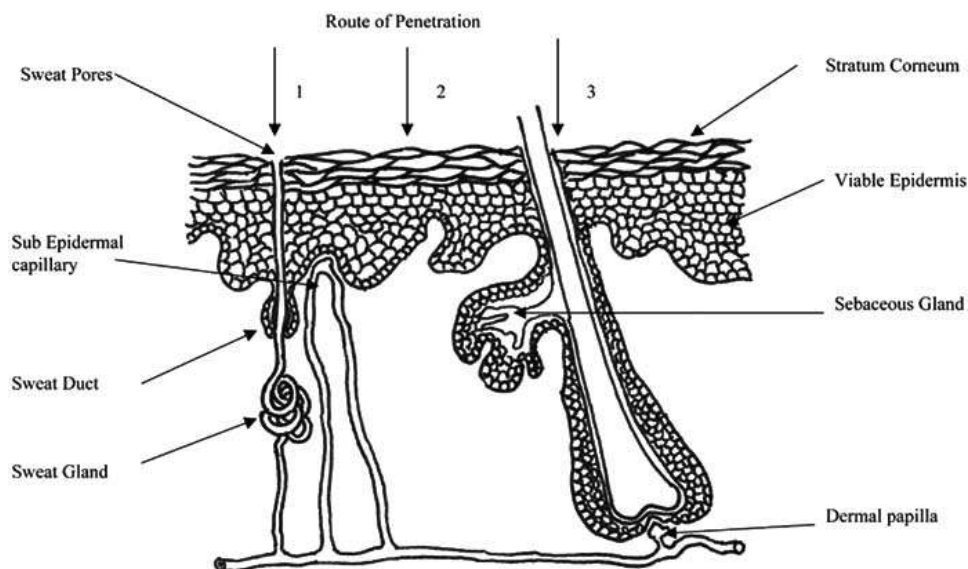


Figure 1: Simplified representation of skin showing routes of penetration: 1. through the sweat ducts; 2. directly across the stratum corneum; 3. via the hair follicles. (Picture retrieved from Benson, 2005)

Pathan and Setty (2009) reported that the *stratum corneum* is 10 to 20 cell layer thick over most of the body. Each cell is a flat, plate-like structure - 34-44 μm long, 25-36 μm wide, 0.5 to 0.20 μm thick - with a surface area of 750 to 1200 μm^2 stacked up to each other in brick like fashion. *Stratum corneum* consisted of lipid (5-15%) including phospholipids, glycosphingolipid, cholesterol sulfate and neutral lipid, protein (75-85%) which is mainly keratin.

2.1.1 Chemical Penetration Enhancers

Currently, the most widely used approach to drug permeation-enhancement across the *stratum corneum* barrier is still the use of chemical penetration enhancers (CPE). CPE are present in a large number of transdermal, dermatological and cosmetic products to aid dermal adsorption of curatives and aesthetics (Karande *et al.*, 2005). Shah (1994) outlined the general effects of various enhancers on the skin, formulation, and the drug. According to Shah, enhancers increase the diffusivity of the drug in the skin by causing *stratum corneum* to undergo lipid fluidization. The decreased barrier function (a reversible reaction) of *stratum corneum* resulted to a reservoir of drug within the skin. CPE increase and optimize the thermodynamic activity of the drug in the vehicle and the skin. It also affects the partition coefficient of the drug, increasing its release from the formulation into the upper layers of the skin. These showed that enhancer interacts and solubilizes the components of *stratum corneum* lipids while the *stratum corneum* retaining its barrier functions (Kang *et al.*, 2006).

According to Kanikkannan *et al.* (2000), CPE increase skin permeability by reversibly altering the physicochemical nature of *stratum corneum* to reduce its diffusion resistance. These compounds increase skin permeability by increasing the partition coefficient of the drug into the skin, thus elevating the thermodynamic activity of the drug in the vehicle. Some factors that influence the delivery of drug through the skin are such as thermodynamic activity of the drug in the CPE formulation, and interaction of the drug and the CPE formulation with the skin.

By using more than 100 CPEs representing several chemical functionalities, Karande *et al.*, (2005) reported on the fundamental mechanisms that determine the barrier disruption potential of CPEs and skin safety in their presence. Their fourier transform infrared spectroscopy studies revealed that regardless of their chemical make-up, CPEs perturb the skin barrier via extraction or fluidization of lipid bilayers. Irritation response of CPEs, on the other hand, was determined correlated with the denaturation of *stratum corneum* proteins, making it feasible to use protein conformation changes to map CPE safety in vitro. Most interestingly, the understanding of underlying molecular forces responsible for CPE safety and potency revealed inherent constraints that limit CPE performance.

Notman *et al.* (2007) found that oleic acid (OA) has a very good capability as a penetration enhancer using computer simulation. They found that OA disperses homogeneously into the lipid bilayer. The polar part of OA interacts with the